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A Reliable Multikilogram-Scale Synthesis of 2-Acetamido-5-Vinylpyridine Using Catalytic BINAP in a Modified Heck Reaction

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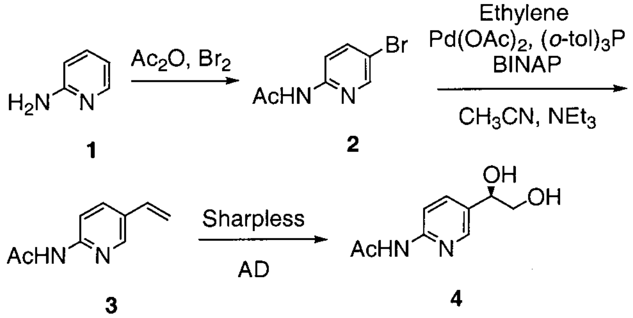
Abstract:

An optimized Heck ethylenation of 2-acetamido-5-bromopyridine using a unique catalytic combination of phosphine ligands, tri-*o*-tolylphosphine and BINAP (*S*-(−)- or racemic) as an additive/promoter is described. The best conditions for ethylenation were determined to be 1 mol % of palladium acetate, 3.3 mol % of tri-*o*-tolylphosphine, 0.25 mol % of BINAP and 180 mol % of triethylamine in acetonitrile at 90 °C. In optimizing the reaction, the purity of the tri-*o*-tolylphosphine was critical. The reaction time was extended by 3-fold when lower purity phosphine was used. The final process was carried out on 46.5 mol of 2-acetamido-5-bromopyridine, providing 71.6% of the corresponding vinyl-substituted pyridine adduct.

The palladium-catalyzed olefination of aryl and vinyl halides or halide equivalents, also known as the Heck reaction, has been extensively used for the synthesis of carbon−carbon bonds.[1] As shown in Scheme 1, optically active diol (**4**), a key intermediate in the synthesis of a drug candidate, was prepared in three steps from commercially available 2-aminopyridine **1**. The second step in the synthesis was a Heck reaction between bromide **2** and ethylene performed under standard Heck conditions ($Pd(OAc)_2$, $P(o\text{-}tol)_3$, TEA, CH_3CN, 90 °C). The subject of this paper is the effective use of BINAP, in either the enantiomerically pure *S*-(−) or racemic forms, as an additive/promoter with tri-*o*-tolylphosphine in the ethylenation of 2-acetamido-5-bromopyridine **2**.[2]

The yields of the Heck reaction in our pilot plant starting with 40−50 kg of bromide **2** were capricious, ranging from 37 to 66%. Furthermore, in some runs the reaction stopped and required a second and third charge of palladium catalyst and phosphine ligand to consume starting bromide. The poor yields and quality of isolated solids in some cases were due in part to the appreciable aqueous solubility of the olefin and level of impurities, such as the phosphine ligand, which tended to cocrystallize with the product as its amount in the reaction increased.

Scheme 1



One observation that was made after the initial large-scale runs was the deposition of palladium black (Pd^0) on the inside of the tank walls. This reduced palladium was extremely difficult to remove between runs without having to resort to extreme measures, such as reconditioning the Hastelloy 276 surface of the vessel by stirring a slurry of isopropyl alcohol and brine, which effectively provided an abrasive agent to clean the reactor. This lengthy cleaning operation between runs resulted in inefficient processing of bromide **2**. We attributed the formation of this reduced palladium as the primary cause of the reaction's failure to go to completion, and we set out to eliminate its formation.

In light of recent reports where BINAP is used as an efficient ligand in amination reactions of aromatic bromides[3] and in the asymmetric Heck reaction,[4] we reasoned that our olefination might benefit from the catalytic addition of this bidentate additive to the Heck reaction mixture. Although there are many recent examples that employ optically active BINAP in asymmetric Heck reactions to generate tertiary and quaternary centers in enantiomeric excesses (ees) >80%,[4] none of these reports describe a possible synergistic advantage of combining BINAP with various monodentate phosphines.

We began the study with the (*S*)-(−)-antipode since it was available from a previous project for our immediate use. In the initial experiment, 0.5 mol % of (*S*)-BINAP was added

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(1) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518−5526. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581−582. (c) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320−2322. Reviews: (d) Heck, R. F. *Palladium Reagents in Organic Synthesis,* Academic Press: London, 1985. (e) Heck, R. F. *Vinyl Substitutions with Organopalladium Intermediates in Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.3, pp 833ff. (f) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (g) Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH Publishers: Weinheim, New York, 1996.

(2) The use of other bidentate phosphine ligands to promote the Heck reaction was not explored due to time constraints and the fact that catalytic amounts of BINAP were not a major cost contributor to the overall cost of goods in manufacturing the API.

(3) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.***1999**, *576*, 125−146. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.

(4) (a) Shibasaki, M.; Vogl, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, GDR, 1999; Vol. 1, Chapter 14. (b) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1−15. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371−7395.

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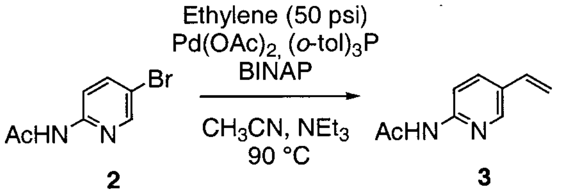
Table 1. **Heck Vinylation of 2-Acetamino-5-Bromopyridine**[a]



entry[b]	additive/ promoter (mol %)	reaction time (h)	product(s) (%SM)	yield (%)	no. of catalyst charges
1	(*S*)-BINAP (0.5)	16	3	57.8	
2	(*S*)-BINAP (0.55)[c]	72	3	28.6	3
3	(*S*)-BINAP (0.55)[d]	16	3	56.6	
4	(*S*)-BINAP (0.25)[e]	16	3	16.8	
5	(*S*)-BINAP (0.10)	16	3/2 (6%)	82.2 (crude)	1
6	(*S*)-BINAP (0.20)	48	3	64.2	2
7	(*S*)-BINAP (0.20)	72	3/2 (1.2%)	66.5	1
8	(rac)-BINAP (0.25)	16	3	64.9	
9	(*S*)-BINAP (0.25)	48	3	68.4	
10	(*S*)-BINAP (0.25)	16	3	67.9	
11	(*S*)-BINAP (0.25)	16	3	71.6	

[a] Unless otherwise noted the catalyst was palladium acetate (1 mol %), the phosphine ligand was tri-*o*-tolylphosphine (3.3 mol %), the additive/promoter was chiral (*S*)-BINAP, and the base was triethylamine. [b] All reactions were carried out with 23.25 mmol of bromide except entry 11 (46.5 mol of bromide). [c] Reaction run in the absence of tri-*o*-tolylphosphine [d] Reaction run in the absence of tri-*o*-tolylphosphine and degassed with N_2 for 10 min prior to pressurizing the Paar bomb with ethylene. [e] Triphenylphosphine used instead of tri-*o*-tolylphosphine and degassed in the same way as entry 3.

to the Heck reaction mixture (1 mol % $Pd(OAc)_2$, 3.3 mol % tri-*o*-tolylphosphine, CH_3CN, TEA) in a stainless steel bomb under 50 psi of ethylene pressure providing the desired product in a respectable 58% yield. The reaction was complete in 16 h as opposed to 3 days in the absence of (*S*)-BINAP and no starting bromide was present in the isolated olefin.

In an attempt to determine the importance of the synergism between tri-*o*-tolylphosphine and (*S*)-BINAP and to probe the lower limit of (*S*)-BINAP that was necessary to drive the reaction to completion, several experiments were performed (see Table 1, entries 2−6). An initial charge of 0.1 mol % of (*S*)-BINAP to the Heck reaction mixture in the absence of tri-*o*-tolylphosphine (entry 2) yielded some product formation after 24 h as evidenced by HPLC analysis.[5] Charging an additional 0.3 mol % of the BINAP generated more product after 48 h, although ∼50% unreacted starting material was still present. With the final addition of another 0.15 mol % (*S*)-BINAP for a total of 0.55 mol % and another charge of $Pd(OAc)_2$ (0.5 mol %), the starting material disappeared after 72 h; however, the olefin was obtained in a disappointing 29% yield.

Degassing the acetonitrile/triethylamine mixture prior to pressurizing with ethylene and adding the (*S*)-BINAP (0.55 mol %) in one portion in the absence of tri-*o*-tolylphosphine nearly doubled the yield to 57% (entry 3).

Using triphenylphosphine in place of tri-*o*-tolylphosphine gave a low yield of product (17%) after 16 h of heating at 90 °C (entry 4). This is in agreement with the generally held belief that the bulkier tri-*o*-tolylphosphine forms a stable PdL_2 species thus minimizing quaternization of the phosphorus with the aryl halide, which can be a problem due to the high reaction temperatures.[6]

Since the BINAP was an expensive component per kilogram in the reaction mixture, attempts were made to determine the lowest level at which it could be employed and yet remain an effective additive (see entries 5 and 6). Thus, in entry 5 the reaction was initiated with 0.1 mol % (*S*)-BINAP. After 24 h the reaction was incomplete by HPLC analysis and an additional 0.1 mol % was added. After 48 h at 90 °C in the bomb, the reaction was complete and provided a 64% yield of the olefin **3**. Adding the BINAP in one portion (0.2 mol %) at the beginning afforded the product in about the same yield (66.5%) but required an extra 24 h to go to completion. This result can be explained by assuming that the first charge of catalyst sequesters reaction by-products that poison the catalyst to some extent, therefore requiring a second charge of catalyst to complete the reaction.

Increasing slightly the amount of BINAP to 0.25 mol % seemed to strike the best balance between reaction time and isolated yield of olefin **3** (entries 7 and 8), albeit this was dependent upon the source of the tri-*o*-tolylphosphine (entry 9).[7] This observation was reduced to practice in the pilot (entry 10) and in a large-scale run (entry 11) using 10 kg (46.5 mol) of bromopyridine **2** with the Elf-Atochem sourced phosphine ligand under the standard conditions to furnish nearly 72% yield of the Heck product in 16 h. Neither BINAP nor tri-*o*-tolylphosphine by itself was as effective in promoting the Heck reaction as the combination of the two.

To our knowledge, there have been no reports using the C_2-symmetrical 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene (BINAP) as an additive with typical monodentate phosphine ligands to enhance the performance of the Heck reaction. However, related reports of the advantage of using bidentate phosphine ligands in Ni-catalyzed asymmetric[8] and nonasymmetric[9] additions of Grignard reagents to allylic acetals are known. In particular, the Hoveyda et al. study reported BINAP to be inferior to (*S*,*S*)-Chiraphos when combined with triphenylphosphine in promoting the Ni-catalyzed asymmetric addition of Grignard reagents to unsaturated cyclic acetals.

In summary, we have developed an efficient and robust modified Heck process to manufacture multikilogram quantities of vinylpyridine **3**. Not surprisingly, (rac)-BINAP, which is considerably less expensive per kilogram than the (*S*)-enantiomer, gave a comparable yield and was also complete in 16 h (entry 8).

Experimental Section

2-Acetamido-5-bromopyridine was obtained from Schweizerhall, Inc and used as received. Tri-*o*-tolylphosphine

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(5) HPLC conditions: Column: Inertsil C-8, 4.6 mm × 150 mm; mobile phase 25% ACN, 75% aqueous buffer (0.1% H_3PO_4, 0.2% TEA); flow rate: 1 mL/min; injection volume: 20 μL.; UV detection at 248 nm.

(6) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427−436.

(7) The custom-made tri-*o*-tolylphosphine (>99% pure) prepared by Elf-Atochem generally gave superior results when compared to the “off-the-shelf” material obtained from SAFC, which is listed as 98% pure.

(8) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650.

(9) Sugimura, H.; Takei, H. *Chem Lett*. **1985**, 351−354.

was purchased from either SAF or Elf-Atochem and used as received. The (*S*)-(−)- and (rac)-BINAP were purchased from Takasago, Inc and Oxford Asymmetry, respectively. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra (400 MHz) were recorded on a Varian Unity 400 spectrometer in $CDCl_3$, and chemical shifts are given in ppm downfield (δ) from internal standard TMS. IR spectra were taken in KBr by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Mass spectra were determined with a Micromass QTOF 2 mass spectrometer using electrospray. High-resolution mass spectra (HRMS) were recorded on a Kratos Profile instrument at 70 ev.

***N*-(5-Vinyl-pyridin-2-yl)acetamide (3).** A nitrogen-purged 100 gal stainless steel vessel was charged with bromide **2** (10 kg, 46.51 mol), tri-*o*-tolylphosphine (467.2 g, 6.27 mol, 0.033 equiv), palladium acetate (104.4 g, 0.465 mol, 0.01 equiv), (*S*)-(−)-BINAP (72.2 g, 0.0025 equiv), and acetonitrile (26 gal). Triethylamine (3.1 gal) was then added via isolated vacuum. The system was repurged with nitrogen and then pressurized to 50 psig with ethylene. The reaction mixture was heated to 90 °C, and ethylene was added to maintain 50 psig pressure. The mixture was stirred overnight (16 h) at 90 °C, at which time TLC (9.8:0.2, methylene chloride/methanol), and HPLC analysis indicated the reaction was complete. The reaction mixture was cooled to ∼40 °C and filtered through Celite. The filtrate was concentrated to a low volume (∼20 gal), and water was added (20 gal). The mixture was again concentrated to 20 gal, heated to 85 °C, and held for 1.5 h. The reaction mixture was cooled to room temperature, and the resulting slurry was granulated overnight. The solid was filtered and resubmitted to another water slurring process. The solid was filtered and slurried in hexanes (5 gal) at 40 °C for 30 min and then cooled to room temperature and filtered again. The product was dried under vacuum at 45 °C to yield 5.4 kg, 71.6% of a white solid; mp 122−124 °C. IR: 3248, 1844, 1687, 1540, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.43 (br s, 1H), 8.31 (m, 1H), 8.22 (s, 1H), 7.91 (m, 1H), 6.65 (dd, $J = 18.0, 10.5$ Hz, 1H), 5.78 (d, $J = 17.4$ Hz, 1H), 5.38 (d, $J = 10.8$ Hz, 1H), 2.26 (s, 3H); MS (ES): *m*/*z* (relative intensity) 163 (M + H, 100); HRMS calcd for 163.0871 (M + H), found 163.0873.

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